REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 13, 14, 19-27, 31, 32, 34 and 36-38 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 13, 14, 19-27, 31, 32, 34 and 36-38 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Ochoa et al. (US Patent 5,296,353) in view of Babbit et al. (US Patent 5,766,920), Ochoa et al. (US Patent 5,443,983), the acknowledged prior art, Wallace et al., Santamaria et al. and Sekine et al. The examiner contends on page 5, first two sentences of the last paragraph, that the claims do not exclude specific antigen stimulation and antigen specific lymphocytes. This rejection is respectfully traversed.

"Lymphocytes from a patient contracting said viral infection", as recited in the present claims, mean lymphocytes which exist in the blood stream of a patient and comprise a wide variety of cells such as virus-antigen specific CD4 and CD8, and naïve CD4 and CD8 that are not sensitized by antigen stimulation. As would be recognized and well understood by one of ordinary skill in the art, most of the lymphocytes are deemed to be specific to virus antigen, and are already activated CD4 or CD8,

i.e., effector cells, because the patient was infected with the virus and contracted the viral infection at the time. The presently claimed invention enables the increase of effector cells by collection of these lymphocytes *ex vivo*, activation with anti-CD3 antibodies, and propagation and cultivation with IL-2. The effect of the effector cells is obtained by injection of the lymphocytes back into the patient. Furthermore, not only CD8 effector cells but also CD4 effector cells play an important role in spreading their effect to a variety of immune cells that already exist in the body when the activated and proliferated effector cells are transfused into the patient. The combined effect is believed to bring about a comprehensive anti-viral effect.

Claims 13 and 14 are now amended to recite the proviso that "said culture medium prepared for culturing *in vitro* does not include a specific antigen for said viral infection". This negative limitation in the amended claims is supported by the positive recitation of the alternative "or the lymphocytes may be stimulated with a specific antigen to be proliferated" in the present specification at page 11, lines 8-12.

As stated in MPEP 2173.01:

> A fundamental principle contained in **35 U.S.C. 112**, second paragraph is that applicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as **>any special meaning

> assigned to a term is clearly set forth in the specification. See MPEP § **2111.01.**< Applicant may use functional language, alternative expressions, negative limitations, or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought. As noted by the court in *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought. (emphasis added)
>
> MPEP 2173.05(i) on Negative Limitations further states:
>
> The current view of the courts is that there is nothing inherently ambiguous or uncertain about a negative limitation. So long as the boundaries of the patent protection sought are set forth definitely, albeit negatively, the claim complies with the requirements of **35 U.S.C. 112**, second paragraph. Some older cases were critical of negative limitations because they tended to define the invention in terms of what it was not, rather than pointing out the invention. Thus, the court observed that the limitation "R is an alkenyl radical other than 2-butenyl and 2,4-pentadienyl" was a negative limitation that rendered the claim indefinite because it was an attempt to claim the invention by excluding what the inventors did not invent rather than distinctly and particularly pointing out what they did invent. *In re Schechter*, 205 F.2d 185, 98 USPQ 144 (CCPA 1953).
>
> A claim which recited the limitation "said homopolymer being free from the proteins, soaps, resins, and sugars present in natural Hevea rubber" in order to exclude the characteristics of the prior art product, was considered definite because each recited limitation was definite. *In re Wakefield*, 422 F.2d 897, 899, 904, 164 USPQ 636, 638, 641 (CCPA 1970). In addition, the court found that the negative limitation "incapable of

> forming a dye with said oxidized developing agent" was definite because the boundaries of the patent protection sought were clear. *In re Barr*, 444 F.2d 588, 170 USPQ 330 (CCPA 1971).
>
> Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984). (emphasis added)

The decision in *In re Johnson* 194 USPQ 196 (CCPA 1977), which is what is currently accepted by the courts and the USPTO, states:

> The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of §112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute. All that happened here is that appellants narrowed their claims to avoid having them read on a lost interference count.
>
> The board indicated that "it is manifestly immaterial" *why* appellants limited their claims. Though it is true that insufficiency under §112 could not be cured by citing the causes for such insufficiency, it is not true that the factual context out of which the question under §112 arises is immaterial. Quite the contrary. Here, as we hold on the

> facts of this case, the "written description" in the 1963 specification supported the claims in the absence of the limitation, and that specification, having described the whole, necessarily described the part remaining. The facts of the prosecution are properly presented and relied on, under these circumstances, to indicate that appellants are merely excising the invention of another, to which they are not entitled, and are not creating an "artificial subgenus" or claiming "new matter." (emphasis added)

In short, such negative limitations, which have basis in the original disclosure only as positive recitations, are permitted.

Applicant however does not believe that "antigen specific lymphocytes" need to be excluded from the claims by recitation, because if the culture medium does not include specific antigen, then the lymphocytes cannot be stimulated by specific antigen but rather are stimulated by anti-CD3 antibodies and IL-2 present in the culture medium.

Ochoa '353 discloses methods of stimulation and propagation of lymphocytes *in vitro*. Although there is disclosure in Ochoa '353 that "it is expected that the methods can be used for cancer or diseases caused by virus", this in no way represents an enabling disclosure of such treatment. Moreover, Ochoa '353 does not teach or suggest an actual step using peripheral blood lymphocytes of a patient contracting the virus infection at the time for treatment in a disease caused by the virus, or an actual preparation step for activated

lymphocytes which are effective in treating a patient contracting a virus infection at the time. This certainly does not provide an enabling disclosure of such a treatment. In order to attempt to satisfy the deficiencies of Ochoa '353, the examiner applies five additional secondary references.

Regarding the cited and applied Santamaria reference, the cells disclosed in this reference are precursor cells obtained from a healthy human who previously suffered from a virus infection and are CMV primed PBMNC. One of ordinary skill in the art would not be motivated to combine Santamaria with Ochoa because the patients infected with CMV in Santamaria are specifically excluded from the instant claims. Furthermore, while the examiner asserts that Santarnaria discloses long term development can be induced and the activated T-cells are of importance in the study of cellular immunology, the presently claimed invention does not include long term development and the present claims do not directly include cellular immunology. Therefore, a person of ordinary skill in the art would not be motivated to combine Santamaria and Ochoa '353. Even if combined, the deficiencies of Ochoa '353 are not satisfied.

Regarding the cited and applied Wallace reference, the cells used in Wallace are also precursor cells. Wallace discloses that precursor cells of T cells can be activated with

IL-2 and that activated T-cells from virally infected patients would be effective when reintroduced into said patient. However, it should be pointed out that the cells which show CTL activity in Wallace are not activated T-cells but are T cell lines established from T cell precursor derived from a seropositive healthy human. In fact, the abstract in Wallace discloses that T cells demonstrated cytotoxicity "even when derived from seropositive donors whose initial cytotoxic response to *in vitro* reactivation was relatively weak". This is evidence for the CTL effect being achieved by establishing cell lines. Therefore, Wallace does not support the effectiveness of activated lymphocytes at reinfusion as asserted by the examiner. Activated lymphocytes are not cell lines. Wallace merely shows the CTL effect of established cell lines *in vitro* against autologous transformed cells. Even if Wallace and Santamaria are combined with Ochoa '353, the deficiencies of Ochoa '353 are not met.

Furthermore, it should be emphasized that Wallace stimulates and activates CTL-precursor lymphocytes (obtained from a seropositive donor who is healthy at the time) *in vitro* using specific antigen (autologous EBV transformed cell) prepared for stimulation. This means that Wallace stimulates and activates memory cells with specific antigen. By contrast, most of the lymphocytes used in the present invention are believed to be effector cells as the lymphocytes are obtained from a currently

infected patient. This means the present invention stimulates effector cells with anti-CD3 antibodies. Wallace differs from the present invention in the cells used and in the stimulation step. Differences in the speed and quality of the resulting effect and the number of increased effector cells which are obtained as a result of stimulation can be easily recognized by one of ordinary skill in the art. Therefore, applicant does not believe it is possible that Wallace discloses or suggests the effect achieved when activated lymphocytes are reinjected back into a patient, as the examiner contends.

The examiner states that Babbit teaches activation of autologous lymphocytes by cytokine which includes OKT3 and IL-2. However, Babbit merely provides a sentence using the phrase "can be used", but does not provide an enabling disclosure for a treatment using OKT3 and IL-2. Even if Babbit, Wallace and Santamaria are combined with Ochoa '353, the deficiencies of Ochoa '353 are not satisfied.

The cited and applied Sekine reference shows that solid-phase anti-CD3 antibody is effective for stimulation and rapid proliferative reaction is induced. However, the intended disease to be treated in Sekine is cancer. Sekine does not disclose or suggest treating virus infection. Although Sekine “infuses” activated lymphocytes into a cancer patient, Sekine does not demonstrate their effectiveness. As illustrated above,

a person of ordinary skill in the art would not be motivated to combine Sekine with Ochoa '353. Even if Sekine, Babbit, Wallace and Santamaria are combined with Ochoa '353, the deficiencies of Ochoa ‘353 are not satisfied.

Ochoa '983 discloses activation of lymphocytes derived from a healthy human and their administration to a different patient with a viral infection. Since the difference between autologous and allogenic lymphocytes is clear to a person of ordinary skill in the art, that same person would not be motivated to combine Ochoa '353 with Ochoa '983. Even if Ochoa ‘983, Sekine, Babbit, Wallace and Santamaria are combined with Ochoa ‘353, the deficiencies of Ochoa '353 are not met.

Furthermore, the effect obtained in the present invention is far beyond that achieved by the combination of Ochoa, Babitt, and Wallace. Combining Ochoa and Babbit, the examiner contends that activated lymphocytes can be used against a viral infection. By further combining the disclosures and teachings of Wallace, the examiner asserts that Wallace supports the effect achieved when activated lymphocytes are reinjected into a patient. However, as discussed above, anti-CD3 antibodies and IL-2, but not a specific antigen, are used for *in vitro* cultivation in the present invention. A much greater variety of cells is thus activated in order to bring out the effect. Accordingly, the effect achieved in the presently claimed

invention is far greater than what one of ordinary skill in the art would expect from Wallace.

The examiner asserts in this rejection that the claims do not exclude antigen specific lymphocytes. However, the present invention is directed to methods (a method for preparing and a method for treating), not a product that includes lymphocytes. According to the common knowledge of one of ordinary skill in the art, lymphocytes in the presently claimed method are effector cells, whereas the cells in Wallace are memory cells. The presently claimed methods do not provide antigen specific stimulation in the culture medium; rather, lymphocytes in the presently claimed method are simply activated with anti-CD3 antibodies and IL-2. A specific antigen for the viral invention is excluded from the culture medium used for *in vitro* activation and this is certainly not obvious to one of ordinary skill in the art. Accordingly, the combination of disclosures and teachings of the cited and applied references cannot lead one of ordinary skill in the art to the presently claimed invention. Moreover, applicants submit that the necessity for combining six different references in order to make a case of obviousness is not only unusual but also unreasonable.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /ACY/
Allen C. Yun
Registration No. 37,971

ACY:pp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\K\koui\Sekine1\pto\2008-10-08amendment.doc